[0117] For therapeutic use the oligonucleotide analog is administered to an animal suffering from a disease modulated by some protein. It is preferred to administer to patients suspected of suffering from such a disease an amount of oligonucleotide analog that is effective to reduce the symptomology of that disease. One skilled in the art can determine optimum dosages and treatment schedules for such treatment regimens.

[0118] For use in diseases modulated by protein that portion of DNA or RNA which codes for the protein whose formation or activity is to be modulated is targeted. The targeting portion of the composition to be employed is, thus, selected to be complementary to the preselected portion of DNA or RNA, that is to be an antisense oligonucleotide for that portion.

[0119] It is generally preferred to administer the therapeutic agents in accordance with this invention internally such as orally, intravenously, or intramuscularly. Other forms of administration, such as transdermally, topically, or intralesionally may also be useful. Inclusion in suppositories may also be useful. Use of pharmacologically acceptable carriers is also preferred for some embodiments.

[0120] This invention is also directed to methods for the selective binding of RNA for research and diagnostic purposes wherein it is useful to effect strand cleavage utilizing enzymatic RNase H cleavage while concurrently effecting modulation of binding affinity and or nuclease resistance. Such selective is accomplished by interacting such RNA or DNA with compositions of the invention which are resistant to degradative nucleases and which hybridize more strongly and with greater fidelity than known oligonucleotides or oligonucleotide analogs.

[0121] Oligonucleotides according to the invention can be assembled in solution or through solid-phase reactions, for example, on a suitable DNA synthesizer utilizing nucleosides, phosphoramidites and derivatized controlled pore glass (CPG) according to the invention and/or standard nucleotide precursors. In addition to nucleosides that include a novel modification of the inventions other nucleoside within an oligonucleotide may be further modified with other modifications at the 2' position. Precursor nucleoside and nucleotide precursors used to form such additional modification may carry substituents either at the 2' or 3' positions. Such precursors may be synthesized according to the present invention by reacting appropriately protected nucleosides bearing at least one free 2' or 3' hydroxyl group with an appropriate alkylating agent such as, but not limited to, alkoxyalkyl halides, alkoxylalkylsulfonates, hydroxyalkyl halides, hydroxyalkyl sulfonates, aminoalkyl halides, aminoalkyl sulfonates, phthalimidoalkyl halides, phthalimidoalkyl sulfonates, alkylaminoalkyl halides, alkylaminoalkyl sulfonates, dialkylaminoalkyl halides, dialkylaminoalkylsulfonates, dialkylaminooxyalkyl halides, dialkylaminooxyalkyl sulfonates and suitably protected versions of the same. Preferred halides used for alkylating reactions include chloride, bromide, fluoride and iodide. Preferred sulfonate leaving groups used for alkylating reactions include, but are not limited to, benzenesulfonate, methylsulfonate, tosylate, p-bromobenzenesulfonate, triflate, trifluoroethylsulfonate, and (2,4-dinitroanilino)benzenesulfonate.

[0122] Suitably protected nucleosides can be assembled into oligonucleotides according to known techniques. See, for example, Beaucage *et al., Tetrahedron*, 1992, *48*, 2223.

[0123] The ability of oligonucleotides to bind to their complementary target strands is compared

by determining the melting temperature (T_m) of the hybridization complex of the oligonucleotide and its complementary strand. The melting temperature (T_m), a characteristic physical property of double helices, denotes the temperature (in degrees centigrade) at which 50% helical (hybridized) versus coil (unhybridized) forms are present. T_m is measured by using the UV spectrum to determine the formation and breakdown (melting) of the hybridization complex. Base stacking, which occurs during hybridization, is accompanied by a reduction in UV absorption (hypochromicity). Consequently, a reduction in UV absorption indicates a higher T_m. The higher the T_m, the greater the strength of the bonds between the strands. The structure-stability relationships of a large number of nucleic acid modifications have been reviewed (Freier and Altmann, *Nucl. Acids Research*, 1997, *25*, 4429-443).

[0124] The relative binding ability of the oligonucleotides of the present invention was determined using protocols as described in the literature (Freier and Altmann, *Nucl. Acids Research*, 1997, *25*, 4429-443). Typically absorbance versus temperature curves were determined using samples containing 4uM oligonucleotide in 100 mM Na+, 10 mM phosphate, 0.1 mM EDTA, and 4uM complementary, length matched RNA.

[0125] The *in vivo* stability of oligonucleotides is an important factor to consider in the development of oligonucleotide therapeutics. Resistance of oligonucleotides to degradation by nucleases, phosphodiesterases and other enzymes is therefore determined. Typical *in vivo* assessment of stability of the oligonucleotides of the present invention is performed by administering a single dose of 5 mg/kg of oligonucleotide in phosphate buffered saline to BALB/c mice. Blood